EQUIPMENT CLEANING

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INTRODUCTION

REGULATORY BACKGROUND

GMP Issues

Cleaning of process equipment has been part of the good manufacturing practices (GMPs) for pharmaceutical manufacturing for many years (1, 2). This has included recommendations for written procedures, cleaning logs, and appropriate design of equipment to facilitate cleaning. Good cleaning practices are necessary to preserve the safety and efficacy of the manufactured drugs and drug products. Possible consequences of inadequate cleaning include cross-contamination (the presence of one drug active in another drug product at an unacceptable level), the presence of foreign material (e.g., a cleaning agent, solvent, or excipient from another drug product), the presence of microbial contamination (numbers and/or species of microbes), or the presence of endotoxins (particularly in parenteral or ophthalmic products). The presence of such contaminants in a drug product may pose safety problems depending on the level of the contaminant. Such contaminants may also affect the efficacy of a drug product; effects could include modifying the bioavailability of the active, the dissolution time of tablets, or the stability of the finished drug. Needless to say, failing to follow GMPs relating to cleaning processes also renders the product "adulterated" and subject to regulatory action.

Expectation of Validation

What is new since about 1990 is the regulatory expectation that certain cleaning processes in pharmaceutical manufacturing be validated. Validation of cleaning processes had been discussed in numerous articles prior to that time (3, 4). However, issues with drug product contamination due to poorly controlled cleaning processes (5), culminating in the Barr Laboratories decision (6), brought this issue to the forefront and clearly established the FDA's authority to require the validation of cleaning processes. As cleaning is a process, the principles of process validation apply to the cleaning process. The Barr decision was followed soon by FDA cleaning validation guidance documents in 1992 (7) and 1993 (8). In 1996, the FDA proposed amendments to the GMPs which clearly defined (if approved) validation of cleaning processes as a GMP requirement (9). The U.S. FDA took the lead in requiring validation of cleaning processes, and other agencies also issued similar requirements. This includes the Pharmaceutical Inspection Cooperation Scheme (PIC/S) document PR-1-99 (10), the Draft Annex 15 to the EU GMPs (11), and the Canadian Therapeutic Products Programme "Cleaning Validation Guidelines" (12). Although the initial emphasis was on cleaning validation related to finished drug products, additional guideline documents clarified that cleaning validation should be considered for active pharmaceutical ingredients (13, 14) and for pharmaceutical excipients (15).

Applicability of Cleaning Validation

It should be noted that these cleaning validation requirements apply only to *critical* cleaning processes. Although GMPs require the cleaning of (and cleaning SOPs for) floors, walls, and the outside of process vessels, such processes are not considered critical cleaning processes. The processes that are critical generally include processes for cleaning product-contact surfaces of equipment or utensils. It is these product-contact surfaces that have the possibility of *directly* contaminating the next product made in the same equipment. In addition, the cleaning of nonproduct-contact surfaces that could reasonably *indirectly* contaminate subsequently manufactured products should also be considered for cleaning validation. For example, some companies have, either on their own or because of regulatory requirements, validated the cleaning of internal surfaces of lyophilizers used for production. On the other hand, validation of cleaning between lots of the same product is not necessarily a requirement (16). This is based on the fact that cross-contamination of the active is not an issue. However, other concerns such as contamination with degradation products, with cleaning agent residues, or with microorganisms may suggest that such cleaning is critical, and therefore should be validated.

CLEANING PROCESSES

The overall cleaning process comprises the soiled equipment, a cleaning method with the associated cleaning equipment, a cleaning agent(s), and process parameters (time, temperature, etc.). These factors should all be captured in a cleaning standard operating procedure (SOP).

Equipment Design

As regards the equipment to be cleaned, this depends on both the equipment itself and the residues to be removed. Ideally the equipment to be cleaned has been designed with cleaning in mind. Design characteristics may be different for manual versus automated cleaning. The equipment design may also affect the extent of disassembly of the equipment as part of the cleaning process. Design characteristics that help maximize cleaning include minimizing deadlegs, minimizing cracks and crevices where soils can be trapped, improving accessibility of the cleaning solution to difficult-to-clean portions of the equipment, and providing adequate drainage. Materials of construction should be selected for the equipment based on the expected cleaning process; such materials may affect both chemical (such as acids, alkalis, and solvents) and physical (such as temperature) compatibility. Although it is difficult to cover all the possibilities because of the varieties of equipment to be cleaned, the principle is the same—the selection of the cleaning process will be limited by the original equipment design (except to the extent that such designs can be modified).

Cleaning Methods

Although cleaning methods are sometimes divided into clean-in-place (CIP) and clean-out-of-place (COP) applications, it may be more useful to consider two significant features of cleaning methods to provide broad categorizations of cleaning processes.

Extent of automation

One factor involves the extent of automation. At one extreme of the "automation" continuum is the fully automatic process—no operator intervention is required for preparation of the cleaning solution, for the cleaning cycle, or for any disassembly or reassembly. The only operator requirement might be pushing a button at the beginning of a cycle, recording the cleaning process in the cleaning log book, and perhaps a visual examination as part of the monitoring procedure at the end of cleaning (and/or before the manufacture of the next product). At the other extreme is the fully manual process. The operator is required for preparation of the cleaning solution, for isolating the system to be cleaned, for applying the cleaning solution, perhaps for applying mechanical action through brushes or wipers, for rinsing the system, and for monitoring process parameters (including the timing of all events). It should be clear that in between these two extremes are various semiautomated processes, which could cover a broad continuum.

Extent of disassembly

A second continuum for cleaning processes involves the degree of disassembly (and consequent reassembly). At one extreme is equipment that requires no disassembly at all (true "clean-in-place"). At the other extreme is equipment that requires disassembly of each component part for cleaning. Disassembly (and reassembly) is preferably avoided for several reasons, including the time it adds to the overall cleaning process (equipment downtime), the concern over damage to the equipment because of stresses during the disassembly/reassembly process, and the concern over incorrect reassembly. However, it should be recognized that there are situations in which partial or complete disassembly of equipment might be required. This includes the removal of filters prior to cleaning, or the opening of a process vessel for placement of a spray device of a portable CIP system into the vessel.

Simplification of cleaning processes

Design of a cleaning process must be taken into consideration not only the nature of the process itself but also the engineering design of the equipment to be cleaned, the various products manufactured in the equipment (such products become "soils" to be cleaned at the end of manufacturing), and the cleaning process parameters (discussed in more detail later). In many pharmaceutical facilities, the objective is to make the process as simple and universal as possible so that one cleaning SOP can be used either for all manufactured products made in the same equipment or for all equipment cleaned in the same process. This simplifies documentation and training and may (because of grouping or bracketing strategies) simplify validation.

Cleaning process steps

The general steps or stages of most cleaning processes involve the following:

Disassembly and isolation: This involves preparation of the equipment for application of the cleaning

solution(s). Disassembly may involve complete disassembly for washing individual parts elsewhere, or may involve partial disassembly, such as removal of filters for separate cleaning elsewhere. The preferred technique for cleaning is to isolate the equipment (or parts thereof) and then clean the entire isolated portion. In a validated process, it is difficult to clean only one portion of a piece of equipment without isolating it (for example, trying to clean a storage vessel only to the level of product in the vessel; the entire vessel, including the vessel dome, should be cleaned).

Prewashing (or prerinsing): In aqueous cleaning, this involves flushing all parts of the system with water (usually at ambient temperature) to physically remove soils that can be readily removed by a flowing water stream. The purpose of the prewash is to minimize soils on the surface for the cleaning step. In this manner, the action of those cleaning agents in the cleaning step are focused on residues that are more tenaciously bound to the surface. In biotechnology manufacture or any manufacture that involves proteinaceous deposits, a second objective of this prewash is to prevent "setting" of those proteinaceous deposits when they are immediately cleaned with a hot water solution. If the cleaning process uses a CIP system, the prewash step is usually a "once through to drain" rather than a recirculating process. The objective is to immediately remove loosely bound soils and discharge them from the equipment rather than to spread them evenly over all equipment surfaces (which would occur to a certain extent in a recirculating system).

Washing: This involves application of the cleaning solution (which may be plain water, but which usually involves some cleaning agent) to all equipment surfaces to effectively remove those soils not removed by the prewash. The washing step may involve continuous application of fresh cleaning solution (such as in a non-recirculating CIP system or in a manual application using a high pressure spray hose), a recirculating application of the cleaning agent in which partially "depleted" cleaning solution is reapplied to surfaces (as in a recirculating CIP system or an automatic machine parts washer), or a static soak of equipment or utensils. The purpose of the washing step is to either dissolve, solubilize, emulsify, suspend, or chemically affect the soils on the surface so they can be readily removed from the equipment either in the washing step (in a non-recirculating process) and/or the rinse step.

Rinsing: The rinsing step is designed to remove both washing solution and associated soluble, solubilized, emulsified, or suspended soils from the equipment. For solvent cleaning, the rinsing solution is usually a fresh application of the same solvent used for the washing step. In aqueous processing, the rinsing solution is usually water. The rinsing step should usually be a non-recirculating application of the rinsing solution. A general rule of thumb followed for finished product manufacture involving aqueous-based drug products is that the quality of water used in the final rinse should be at least as good as the quality of water used in the manufacture of the next product. The rationale behind this is that any water contaminants in the final rinse left behind on equipment surfaces by the final rinse are identical in quality to water used in manufacturing of the next product. If the drug does not contain water, such as in the manufacture of a synthetic organic active substance, there may be other considerations for the selection of the quality of the final rinse water. A common practice in bulk pharmaceutical manufacture, suitable for most applications where aqueous cleaning is performed, is to use deionized water as a final rinse.

Drying: Drying is an optional step. One factor in whether drying should be done is the time period before the next use of the equipment. Equipment that is to be used immediately (within a few hours) may not have to be dried, particularly if the equipment is effectively drained to minimize any dilution effect of residual rinse water or solvent. However, the effect of residual water on microbial proliferation during extended storage is a significant issue. Options for drying include heated (and optionally filtered) air and the use of a final alcohol/water rinse. The final alcohol/water rinse may also further reduce the bioburden due to the antimicrobial action of the alcohol. This use has to take into consideration the flammability of such a mixture.

Reassembly and storage: These should be part of the cleaning SOP. "Reassembly" may involve removal of temporarily installed cleaning equipment (e.g., the spray device of a portable CIP unit) or reassembly of equipment parts themselves. If the equipment is to be stored for a significant time before reuse, critical elements for storage include whether the equipment is dry, physical protection of equipment from recontamination by use of items such as plastic wrapping, and the room conditions (air quality, temperature, and humidity) where the equipment is stored. Typically it is expected that stored equipment will be tagged as cleaned with an expiration (or "use by") date. Expiration dates for stored equipment are established based on the possible routes and extent of recontamination during storage. For storage, the focus of regulatory agencies is microbial contamination; however, other types of contamination should also be evaluated.

Automated CIP systems

The discussion of CIP processes deserves special comment because of industry trends to use CIP systems. As used in a broad sense, CIP refers to any system in which the equipment is cleaned with no or minimal disassembly. In a

more narrow sense (and in this sense it is more commonly used now), CIP is used to refer to systems in which one or more spray devices is placed in the equipment to be cleaned. A control unit, comprising a pump, associated valves, and a PLC (programmable logic controller), pumps a cleaning solution from a storage tank through the spray device(s). The spray device(s) is engineered and placed so that solution is either directly sprayed or else sprayed so that the solution cascades down the equipment sidewalls to cover all surfaces of the equipment for effective cleaning. In a non-recirculating CIP system, the cleaning solution passes once through the process vessel and associated piping, and then goes to drain. In a recirculating system, the cleaning solution passes through the process vessel and associated piping and then back to the cleaning solution storage tank. It is then pumped through the spray device again, for multiple passes.

The spray device may be either permanently mounted in the process vessel, or installed for cleaning and then removed for product manufacture. Spray devices may be stationary. Stationary spherical devices, the most common type, are called "spray balls." Spray balls are usually stainless steel hollow spheres in which holes are drilled. The placement of the holes is designed to provide adequate coverage for the vessel to be cleaned. Stationary spray devices are usually considered "sanitary" because they are self-draining. The other type of spray device is a dynamic (or rotating) spray device. These are similar in principle to a stationary spray device (they are designed to distribute cleaning solution over all surfaces of the process vessel) except that dynamic spray devices will rotate in one or more planes to provide more even distribution of the cleaning solution. Dynamic spray devices also typically operate at high spray pressures, so that the impingement of the cleaning solution on the vessel surfaces provides more mechanical energy to help dislodge residues. Dynamic spray devices are typically not mounted permanently because they are not self-draining (and thus sanitary); however, some newer dynamic devices are claimed to be sanitary.

A key to operation and validation of a spray device is to perform a "coverage" test, such as a "riboflavin test." Riboflavin is readily water soluble, and also fluoresces under an ultraviolet light. Such a test involves spraying the interior surfaces of the equipment with a dilute solution of riboflavin. A short CIP rinse cycle is then performed using just water in a non-recirculating mode. Following this, the interior surfaces are examined using an ultraviolet light source. If any surfaces fluoresce green, it is an indication that solution coverage in those areas may be inadequate. Poor coverage should require a redesign of the spray device system, either by adding additional spray devices, using a different spray device, or by drilling additional holes in a stationary spray ball. Such a modified spray system should be retested for adequate coverage. Such riboflavin testing is usually part of the operational qualification (OQ) of the equipment.

Cleaning Agents

Aqueous vs. nonaqueous

In addition to the cleaning method used, the cleaning agents used in the washing step are critical. It should be appreciated that selection of the cleaning method and cleaning agent(s) are somewhat interdependent. Selection of a cleaning method may limit the available cleaning agents that can effectively be used in that process. For example, a CIP process requires a low foaming aqueous cleaning agent, while extent of foam may not be critical for manual cleaning. Cleaning agents may be divided into aqueous and nonaqueous cleaning products. Nonaqueous products are typically solvents, and are more common in cleaning in the bulk manufacture of an active pharmaceutical ingredient (API). Typically, the solvent used for cleaning is the same as that used for manufacture. The cleaning effectiveness depends on the solubility of the residue(s) in the solvent at the temperature of cleaning. Particularly for cleaning of distillation columns, refluxing with a volatile solvent is a common practice for effective cleaning. The trend in the manufacture of APIs is to move away from solvent cleaning to aqueous cleaning. However, it should recognized that in many cases this not practical, and even if it is, the aqueous cleaning may be followed by one or more solvent flushes to remove the water from the process vessels.

Types of aqueous cleaning agents

Aqueous processes involve cleaning with water and, optionally, other ingredients to assist in the cleaning process. If aqueous cleaning can be suitably performed, it is preferred over solvent cleaning because of cost issues (including the cost of the solvent as well as the costs of disposal or reclamation of the solvent) and because of environmental issues relating to the use or emissions of solvents. In aqueous processes, the use of water alone should be considered because it eliminates the concerns over having to consider potential contaminants from the cleaning agent during cleaning validation. However, in most cases, the performance characteristics of various aqueous cleaning agents more than overcome the concerns about cleaning agent residues (particularly if the cleaning agents selected are free-rinsing). The successful use of water alone for the washing step depends solely on the

solubility of the residues in water at the temperature of cleaning, and may not typically provide other cleaning mechanisms such as emulsification and dispersion. Therefore, use of water alone may not meet other cleaning objectives such as short processing times.

Another option for aqueous cleaning involves the use of commodity chemicals, including alkalis such as sodium or potassium hydroxide, acids such as phosphoric or citric acid, or sodium hypochlorite solution. These are typically diluted in water at levels of 0.05–1% (w/w), and the resultant solution is typically used at elevated temperatures (45–80°C). Commodity chemicals may provide better cleaning than water alone, and they do so at a relatively inexpensive cost. Residue detection of cleaning agents during validation is relatively straightforward because there is usually only one chemical species to detect from the cleaning agent itself.

A third option for aqueous cleaning is to use a formulated cleaning agent. These formulated products usually contain several functional agents including a surfactant(s), an alkalinity or acidity source, water miscible solvents such as glycol ethers, dispersants such as low-molecular-weight polymers, and various builders such as chelants. The main advantage of such formulated cleaning products is that they are multifunctional because of the variety of components; each component broadens the performance in terms of being applicable on a wider variety of soil types. Well-formulated products thus enable a pharmaceutical manufacturer to use one cleaning agent in one cleaning SOP to effectively clean not only the variety of components in a finished drug product, but also a broader range of finished drugs themselves. It should be noted in the former case that for many (if not most) finished drugs, it is the excipients in the finished drug that are more difficult to clean (as compared to the cleaning of the active ingredient). However, the selection of a formulated cleaning product necessitates that the pharmaceutical manufacturer knows the ingredients in the product, both as a check on the consistency of the formulation over time and to effectively establish residue limits for the cleaning agent.

Basis of selection of cleaning agent

The selection of an aqueous cleaning system is simplified if only water alone, or water and a commodity chemical alone, are used. The cleaning performance can be somewhat predicted based on solubility characteristics (at the appropriate pH) or by consideration of the peptizing performance of alkalinity on protein or the oxidizing action of sodium hypochlorite on denatured protein. In the case of formulated multifunctional cleaning agents, the performance is more difficult to predict based on chemistry alone, and an acceptable cleaning agent is preferably selected based on experience or on laboratory studies. The selection of cleaning agents is also complicated by the fact that sometimes proper cleaning necessitates the use of two cleaning agents at the same time (a primary cleaning agent and a functional additive of some sort), or by the use of two cleaning agents in succession (for example, the use of an alkaline cleaning product followed by an acidic cleaning product).

Cleaning Parameters

While selection of the cleaning method and cleaning agent(s) is important, equally important are the various parameters to consider in the overall cleaning system. These include cleaning process parameters as well as parameters related to the system actually cleaned. Probably the most important cleaning process parameters are the time of cleaning, the temperature of cleaning, the concentration of the cleaning agent, the water quality, the impingement action of the cleaning solution, and any mixing in the cleaning solution.

Time

Three aspects of time are important to the cleaning process. The first is the time from the end of product manufacture to the beginning of the cleaning process. This is important in validated cleaning because the nature of the soil to be cleaned may change over time. Changes may include the drying of the soil residue (thus possibly making it more difficult to clean) or microbial proliferation (thus increasing the bioburden to be cleaned during the cleaning process). A maximum time between the end of manufacture and the beginning of the cleaning process must be specified, and this maximum time must be considered in the selection of worst case conditions for the validation of cleaning processes. A second aspect of time is the times of the cleaning process steps, as well as the time between steps. This includes specifying the time of the prewash, of the washing step, and of rinsing. These are usually established based on laboratory and scale-up trials in the development of a cleaning SOP. The times between these three steps may be critical; if so a maximum time interval should be specified. For example, in the manual cleaning of larger equipment, the time interval between the washing step and the rinse could be significant if the cleaning agent on the washed part is allowed to dry before the rinsing step starts. Drying after the washing step may redeposit soils and prevent effective rinsing. The expectation for validated cleaning is that the times for the various phases are specified. It is generally unacceptable to specify an open-end time frame such as

"test until clean" (that is, continue repeating the cleaning process until tests indicate the equipment is clean) in a validated process. Such performance is indicative of an uncontrolled cleaning process. The third aspect of time is the time of storage of cleaned equipment. Although recontamination of equipment is generally known to be event related rather than time related, time is known to affect microbial proliferation. For this reason it is expected for validated cleaning processes that an expiration date (or "use by" date) for cleaned equipment be established.

Temperature

A second important process parameter is the temperature, not only of the cleaning solution, but also of the prewash and rinse solution. The solution temperature can significantly affect cleaning performance, including the rate of solubility and the extent of hydrolysis. Control of temperature during cleaning is preferable. However, it should be recognized that consistency is more important than just constancy of temperature. A consistent decrease in temperature (due to the lack of a heat exchanger in a cleaning circuit) may be acceptable for validated cleaning, provided that the decrease in temperature is consistent from one cleaning event to the next. Temperature of the prewash is generally ambient to prevent setting of certain residues at higher temperatures. The temperature of the rinse is probably least critical. However, it should be recognized that the higher temperature of a rinse might facilitate faster rinsing. In addition, if the temperature of a first rinse is significantly lower than the temperature of the cleaning solution, the temperature "shock" may cause a cleaning solution containing emulsified soils to "break," thus redepositing soils on the equipment surfaces. Temperature should be controlled within reasonable limits, for example, within 5°C of the control point.

Cleaning agent concentration

Cleaning agent concentration should be specified and controlled. Cleaning agent concentration can usually be controlled by diluting based on weight or volume, or by diluting to a known control point, such as to a known conductivity. Within reasonable limits for aqueous cleaning, higher cleaning agent concentrations result in more effective cleaning. Concerns with higher cleaning agent concentration include deleterious effects on equipment and safety issues in manual cleaning.

Water quality

In certain circumstances, water quality can be critical for cleaning performing. If the washing step involves the use of surfactants for cleaning, the presence of hard-water ions (calcium and magnesium) is well known to interfere with effective detergency. Additionally, in the presence of alkalinity sources (which raise the pH), calcium ions will precipitate as calcium carbonate. Such deposits, if not removed from the equipment surfaces, can contribute to the equipment being judged visually dirty. Some formulated cleaners will contain chelants (such as salts of ethylenediamine tetra-acetic acid) to minimize such possibilities. For most cleaning applications, pharmaceutical manufacturers will also use the same quality of water (Purified Water or Water for Injection) that is used for manufacture of the drug product. Lesser quality water, such as tap water, can be used provided the water quality (both chemical and microbiological) is carefully monitored. In addition, if the tap water quality may vary (due to seasonality or source, for example), the worst-case water conditions must be considered for validation purposes.

Impingement

The impingement of the cleaning solution refers to the physical action of a cleaning solution as it hits the surface from a spray application. Such a spray application may include that from a spray device in a CIP system, or may be from a high-pressure hose spray application. Impingement provides mechanical action to help dislodge residues from surfaces. Such impingement can be beneficial if the dislodged residues can then be suspended, emulsified, or otherwise carried away from the equipment surfaces and removed from the cleaning system. Dislodging residues and just displacing them to another location on equipment surfaces may not prove beneficial. In some circumstances, impingement with a solution containing added cleaning agents may be preferred.

Mixing

Mixing refers to the movement within the cleaning solution itself. With a static application of a cleaning solution, as the soils on the surfaces dissolve, emulsify, or otherwise migrate into the cleaning solution, a concentration gradient of saturated or partially saturated cleaning solution is established near the equipment surfaces. This concentration gradient minimizes the chemical cleaning action. Mixing eliminates this concentration gradient and places fresh cleaning solution (or at least a less saturated cleaning solution) in contact with soils on surfaces. This optimizes the cleaning process. It is desirable that mixing be such that the cleaning solution experiences turbulent flow.

The six parameters discussed above are parameters that usually can be controlled by proper design of the cleaning process. Other parameters that are important for cleaning are things that are controlled more by equipment design or by manufacturing process design. Those characteristics

include the nature of the equipment surfaces, the physical nature of the soil, and the amount of soil.

Nature of the surface

In removing manufactured product soils from equipment, the nature of the surface may also affect the cleaning process. This includes any special factors in the adhesion of the soil to different surfaces. Different surfaces include differences in type, such as stainless steel, glass, and various plastics. Effective removal of soils from all representative surface types is usually considered in a sampling plan for cleaning validation. Different surfaces also include the roughness or smoothness of the surface itself. Although there is controversy on this, as a general rule for most surfaces involved in pharmaceutical manufacturing, smoother surfaces are more easily cleaned. This may be related to the fact that rougher surfaces have cracks or crevices where soils can more easily "hide." For example, etched glass surfaces are generally more difficult to clean as compared with highly polished glass surfaces. A third factor in considering the nature of the surface is the chemical or physical compatibility of the cleaning solution with the surface itself. The objective in cleaning is to remove the soils and restore the surface to its original condition (or as close to that condition as practical). Two examples of substrate compatibility issues are the repeated use of high levels of hypochlorite on stainless steel (leading to rouge formation) and the use of high levels of aqueous alkalis (sodium or potassium hydroxide) at high temperatures for prolonged periods on glass-lined vessels (leading to etching of the glass surfaces). Other issues might be temperature compatibility of plastics or of gasket materials. Although some deleterious effects may be expected in any cleaning process, the process should be designed to clean effectively and yet keep substrate compatibility issues to a minimum.

Condition of soil

A second factor to consider is the soil condition itself. Three "states" of the soil may be considered—freshly deposited soil, dried soil, and baked-on soils. The difference between the last two is that drying just involves the removal of water without any chemical changes in the soil. Baking usually involves not only the removal of water but also a significant chemical change in the soil. Such chemical changes usually result in the soil being more difficult to remove. For example, drying sugar on a surface may render it slightly more difficult to remove; however, baking it at elevated temperatures will caramelize the sugar and render it extremely difficult to remove. The condition of the soil may change because of manufacturing process conditions, such as product splashing onto a vessel dome that is steam jacketed and baking onto the surfaces. It also may change because of a time delay after manufacture and before cleaning, allowing the product to dry out. It should be noted that merely drying of certain polymers on surfaces might render them extremely difficult to remove. For example, dried solutions of carboxymethylcellulose (CMC) can be extremely difficult to remove from surfaces.

Although it may be difficult to control the extent of drying or baking in certain processes, these phenomena should be evaluated, and if they do occur, the cleaning process should be designed to remove those soils in the more difficult dried or baked conditions.

Amount of soil

A third factor to consider is the amount of soil on the surface. As a general rule, the greater the amount of soil on the surface, the more difficult the cleaning. For freshly deposited soils, this may not be a serious issue if the bulk of the soil can be readily removed in the prewash. On the other hand, with dried or baked-on soils, the prewash may have little benefit in reducing the amount of soil on the surface. Unfortunately, surfaces that are most likely to have larger amounts of soils (dead legs, cracks, crevices, low flow areas) are also those that are more difficult to clean because of accessibility of the cleaning solution to the surfaces. For cleaning process design purposes, worst cases in soil amounts should be considered.

CLEANING STRATEGIES IN LIGHT OF VALIDATION

Although cleaning processes should be primarily based on what is necessary for good cleaning, they may be modified somewhat based on the regulatory needs for validation. As most pharmaceutical companies will want to validate a cleaning process and not have to do additional significant revalidation work in the near future, this may limit the selection of cleaning agents. As a key part of any validated process is consistency and control, cleaning SOPs for validated processes will also generally have more detail and specificity.

Cleaning for Multiproduct Equipment

Several strategies are possible for cleaning of equipment used to make two or more different products. One option is to optimize a cleaning process for each product made on the equipment. This may mean different cleaning agents for cleaning after each manufactured product, although usually what it means is that the same cleaning agent is

used under different process conditions (such as time and/or cleaning agent concentration). Each manufactured product will have its specific cleaning SOP. Another option is to use only one cleaning process for all products manufactured on that individual piece of equipment. One cleaning SOP (with all process conditions the same) is used for all manufactured products. Such a strategy allows for the possibility of "grouping" or "bracketing" for validation protocol purposes. However, it should be recognized that the decision to use one cleaning SOP for all manufactured products has implications for both cleaning and for validation purposes. A strategy of "one SOP for everything" has advantages for cleaning in terms of simplifying documentation and simplifying training. However, such a strategy can be pursued regardless of whether one adopts grouping strategies for validation or not. Clearly, one can also adopt a hybrid strategy, in which several manufactured products are cleaned with one SOP and another group of products (manufactured on the same equipment) is cleaned with a different SOP.

Cleaning in Campaigns

Cleaning between lots of the same product made successively on the same equipment in a campaign may allow for less aggressive cleaning procedures. The reason is that in such cleaning there is no concern about cross-contamination with an active from a different product. However, there are concerns about cleaning. First is the issue of lot integrity—how much of the active or product from one lot can comingle with a different lot and be considered different lots for such purposes as recalls? In addition, while cross-contamination is not an issue, other issues such as contamination from residues of cleaning agents and microbial contamination should also be considered. Another issue in campaigns in which cleaning is minimal is the possibility of degradation product accumulating on the equipment.

VALIDATION ISSUES

IQ/OQ/PQ

Cleaning validation is a type of process validation, and the principles of process validation (17) apply equally to a cleaning process. This includes installation qualification (IQ), operational qualification (OQ), and process or performance qualification (PQ). IQ and OQ should focus on the equipment used for the cleaning process, such as a CIP skid, a spray device, or the monitoring equipment (such as a conductivity probe). PQ involves performance of the cleaning procedure three consecutive times and evaluating the success of the cleaning procedure, usually by measuring the amount or degree of potential contaminants on the cleaned equipment surfaces. The cleaning SOP should be challenged during the three PQ runs, using (as much as possible) process conditions within the normal ranges that are more likely to induce failure. For example, if the time from the end of manufacture until the beginning of cleaning is specified as a maximum of 12 h, then at least one of the PQ runs should be performed at that maximum time to demonstrate adequate performance.

Cleaning validation is different from other types of process validation in that with cleaning validation both the product cleaned as well as the next product manufactured must be considered. The cleaning SOP is primarily based on what is required to remove the manufactured product. However, the types and acceptable levels of residues following cleaning are also determined by the nature of the next product manufactured in the cleaned equipment. For this reason, cleaning validation is more dependent on what other products are made on the same equipment. Furthermore, the addition of a new product to equipment previously validated for cleaning with multiple manufactured products requires a reevaluation of that previous validation work to determine whether or not the previously validated residue acceptance limits are still applicable in light a new "next product."

Residue Limits

Validating a cleaning process includes selecting target residues and setting limits for those residues following the cleaning process. Target residues are selected based on possible residues that can be left after the cleaning process. This requires an understanding of the cleaning process, and may require an investigation into possible degradation products that may occur during the cleaning process. Acceptable levels of those specific residues are based on what could occur should those residues contaminate the subsequently manufactured product (18, 19). Analytical determinations of residues are usually required. In addition to those measurements, it is expected that the equipment will be visually clean. Examination of equipment for visual cleanness requires training of the observers and may require auxiliary lighting. A visual examination may be supplemented by use of a video camera for recording purposes or by use of a boroscope for pipes. In some cases, equipment may be disassembled for visual examination (and optionally for analytical sampling) to determine cleanness.

Limit in next product

It is important in any discussion of "residue limits" to understand that limits for a cleaning process may be expressed in different ways. This includes the limit of the residue in the subsequently manufactured product, the limit of the residue on the cleaned equipment surfaces, and the limit of the residue in the analyzed sample. These are all related, but they are usually different numbers. For an active ingredient in the cleaning of a finished drug product, the limit in the next product is usually calculated based on application of a safety factor (usually 0.001 or lower) to the minimum daily dose of that active in the maximum daily dose of the subsequently manufactured product. The active or level of active in the subsequently manufactured product is irrelevant unless there is information about unusual deleterious interactions. This calculation is also independent of manufacturing issues such as batch size and equipment surfaces areas, and can be calculated solely on information about the dosing of the two products as follows:

$$L_1 = \frac{\text{MinDA} \times \text{SF}}{\text{MaxDSP}} \tag{1}$$

where L_1 is the limit of the active in the next product, MinDA is the minimum (daily) dose of the active (the target residue), MaxDSP is the maximum (daily) dose of the subsequently manufactured drug product, and SF represents an appropriate safety factor. Care needs to be paid to selection of units; the L_1 limit is usually expressed in μg/g (or ppm).

Limit per surface area

The next limit calculated is usually the limit per equipment surface area. This is calculated based on the limit in the next product, the batch size of the subsequently manufactured product, and the equipment shared surface area. This is expressed as:

$$L_2 = \frac{L_1 \times \text{BS}}{\text{SSA}} \tag{2}$$

where L_2 is the limit per surface area, BS is the batch size, and SSA is the shared surface area. Units should be consistent, and the L_2 limit is usually expressed in units of $\mu g/cm^2$.

Limit in analytical sample

The next limit is the limit in the analytical sample. If the sampling method involves swabbing, the surface area swabbed and the amount of diluent used for desorbing the swab must be considered. The limit per swab sample is then calculated as:

$$L_3 = \frac{L_2 \times \text{SA}}{\text{AD}} \tag{3}$$

where L_3 is the limit per analytical sample, SA is the swabbed area, and AD is the amount of diluent for swab elution. Here again units need to be consistent, and the L_3 limit is usually expressed as μg/g or μg/mL. It should be clear that the limit in the analytical sample can be manipulated by changing the area sampled (higher areas result in larger limits per analytical sample) or the amount of diluent used (lower amounts result in larger analytical sample limits). If a sampling rinse is used (in place of swabbing), SA effectively becomes the total surface area of the equipment, and AD becomes the volume of solution used for the sampling rinse.

Nondose limits

For residues (such as cleaning agents) that do not have a defined dose, some measure of toxicity, such as an acceptable daily intake (ADI), is used for residue limit purposes. If the subsequently manufactured product is an in vitro diagnostic (IVD), and has no defined dose, then some evaluation of the effects of target residues on the performance or stability of the IVD product should be performed. These nondose factors are used only for the L_1 limit; there are no changes for calculation of L_2 and L_3 limits.

Limits for multiple subsequent products

When a residue limit is to be calculated for a product where there may be more than one subsequently manufactured product, calculations should be made to compare the surface area residue limits (L_2 limits) by using each subsequent product. If the manufacturing order is not to be restricted, the cleaning validation of the first product should be established using the lowest surface area limit.

Sampling Procedures

Sampling procedures for cleaned surfaces can be divided into four types. Direct surface sampling involves a fiberoptic probe (such as a near infrared probe) that is placed directly on the surface. An output is provided as to the type of residue and the level. Such systems are currently in development (20), but are not commercially practical. Swab sampling involves wiping a fixed area of the surface with a premoistened swab. The swabbing procedure is designed to remove any residues from the surface, and the swab is then placed in diluent to desorb the residue from the swab to the diluent. The residue is then measured in the diluent by a suitable analytical technique.

Such swabbing is commonly called "direct surface sampling," although it clearly is an indirect measure. Rinse sampling involves flushing the equipment surface with a fixed amount of rinse solution (aqueous or solvent), capturing the rinse solution, and then measuring the target residue in the rinse solution. A true sampling rinse is distinct from the final process rinse, and may involve a solution different from that for the process rinse. A fourth sampling procedure is placebo sampling. This involves making a placebo of the subsequently manufactured product in the cleaned equipment. Following manufacture of the placebo, the placebo is sampled and analyzed for the target residue. Any target residue in the placebo would come from the cleaned equipment, and it could be expected that the level present in the placebo would be the level present in any such subsequently manufactured product. Placebo sampling is not widely used because of regulatory concerns related to uniformity of contamination of the placebo from the equipment surfaces and the analytical challenge of finding low levels of residues in placebos.

Analytical Methods

Relationship to target residue

The analytical method selected to measure the target residue must provide a direct measurement of that target residue. When regulatory authorities first began requesting that cleaning be validated, some companies merely tested the rinse water by USP Purified Water specifications to determine if the equipment was clean. The rationale was that the effluent met the same standard as the incoming water. Regulatory authorities (quite rightly) rejected such arguments (because of the possibility of unacceptable levels of potent drugs being present, and because of the possibility that the target residue not being removed in the rinsing procedure), and requested that analytical techniques target the specific residues of concern. However the requirements for analytical methods for residue determination are slightly different from methods for actives level determination in finished product in one important way. For finished product actives determination, a method is required to unequivocally measure the active in the presence of known potential interferences and provide an exact level of the active present. For cleaning validation residue analysis, it is not so as important to know exactly how much residue is present as to know that the amount present is below the acceptance criteria in the validation protocol. For this reason both specific and nonspecific analytical methods can be used for residue detection purposes.

Specificity of methods

Specific methods are preferred because they can more accurately provide information for evaluating potential problems. Because they are designed to eliminate the effects of potential interferences, they can more reliably meet the acceptance criteria. The most common method for residue determination for cleaning validation purposes is the high performance liquid chromatography (HPLC) procedure. In contrast, nonspecific methods such as total organic carbon (TOC) can only provide an upper limit value of the target residue, provided there are no negative interferences (that is, all interferences contribute positively to the analytical response). For TOC, this is usually the case. If the anaytical response is treated as if the response comes only from the target residue, then an upper limit calculation of the target residue can be obtained. If such upper limit calculation is below the acceptance criterion, then it is safe to claim that the residue is within acceptance limits. Nonspecific methods such as TOC are more commonly used in biotech manufacture, where proteinaceous actives are readily degraded by the cleaning procedure. In such cases, the TOC values are treated as if the carbon were due solely to the protein active. Actually, some of the carbon may be due to the cleaning agent, and some may be due to the excipients or processing aids.

Validation of methods

It is expected that any analytical method chosen be validated, including an evaluation of specificity, sensitivity (limit of detection and limit of quantitation), accuracy, precision, range, and linearity (21). The range validated is preferably a range around the expected value in the analytical sample. However, it is wise to also include values up to the acceptance limit in the analytical sample.

Sampling/Analytical Method Recovery

The sampling method chosen must be challenged in combination with the analytical procedure to determine the recovery of the sampling method. This is typically a laboratory study involving spiking a model surface with the target residue and performing the sampling procedure on the surface and measuring the residue with the analytical procedure (22). The amount of residue measured is compared to the amount spiked to give a percent recovery. Recoveries of greater than 80% are considered good, but recoveries of greater than 50% are acceptable. As the analytical values have to be transformed by the recovery values, it is desirable to obtain as high a recovery as consistently possible.

MICROBIAL CONTROL ISSUES

Issues in Cleaning

GMPs require that procedures be in place to limit objectionable microorganisms in both nonsterile and sterile drug products. This should be interpreted to include both the number of organisms as well as the type (species) of organism. Protection of subsequently manufactured product from microbial contamination can be accomplished in part by effective cleaning, by a separate sanitizing step, and/or by storage procedures. In many cases effective microbial control is achieved by a good aqueous cleaning process. The conditions of cleaning can either physically remove microbes, or these conditions (hot alkaline or acidic aqueous conditions) can be conducive to the destruction of microbes. The use of hypochlorite for removal of denatured proteins also serves as an effective oxidizing biocide. If cleaning alone does not achieve adequate microbial reduction, the use of either a chemical sanitizer or elevated temperature (steam or hot air) can be considered. Chemical sanitizers include hydrogen peroxide, peracetic acid, quaternary ammonium chlorides, and alcohols; as a general rule phenolic sanitizers are not used for process equipment because of the difficulty of rinsing from equipment surfaces. If the sanitizer leaves a residue, then a final rinse should be considered to reduce that residue to an acceptable level. Acceptable levels of microbes in the cleaned equipment can be established depending on the nature of the subsequently manufactured product. Limits for nonsterile products can be established based on accepted levels of microorganisms in nonsterile products. Such calculations usually result in acceptance levels that are considerably above what can be routinely achieved with good cleaning procedures. Limits for equipment surfaces used for manufacture of terminally sterilized products are usually related to assumptions of the maximum bioburden for product sterilization purposes. Limits for equipment surfaces used for manufacture of aseptically produced products are usually related to assumptions of the maximum bioburden for equipment sterilization purposes.

Issues in Storage

One major regulatory issue in the cleaning of equipment is the possible microbial proliferation due to improper storage, such as in a wet condition or with pools of water. The preferred method for dealing with such concerns is to effectively dry the equipment before prolonged storage. An alternative (but less desirable option) is to include an additional cleaning and/or sanitizing step after storage and before the next use of the equipment. If this alternative is used, the measurement of both chemical and microbial residues should be performed at the end of this cleaning/sanitizing step.

VALIDATION MAINTENANCE

Once a cleaning process has been appropriately validated, steps should be taken to help insure that the cleaning process remains consistent and in control. Steps that are taken to help assure this include regular monitoring, a change control system, training, and revalidation.

Monitoring

The testing that is done for routine monitoring of the cleaning process should be distinguished from the testing that is part of PQ process qualification. Monitoring tests are usually done on each individual cleaning run. Tests are selected which could be indicative of a cleaning system that is either out of control, or could be trending out of control. Examples of process parameters that could be monitored include the concentration of the diluted cleaning agent, temperature of the cleaning solution, times of various process steps, pressure at a spray device, flow rates, volumes of solutions used, and conductivity of the final rinse water. As these monitoring steps should be part of the cleaning SOP, they should also be performed during the three PQ runs. Some monitoring can give pass/fail information, which clearly indicates the cleaning process is out of control, requiring an investigation and correction of the problem. For example, a higher than specified pressure at a spray device may suggest that spray nozzles were blocked, and that perhaps cleaning coverage was inadequate. This would require an immediate investigation of whether the equipment was adequately cleaned. Such equipment should not be used until a confirmation of adequate cleaning is performed, and the cause of the high pressure corrected. On the other, hand monitoring of the final rinse water conductivity or TOC may show results which do not necessarily suggest that cleaning was inadequate, but rather may display a trend which suggests that cleaning may become inadequate if such a trend continues. This is the value of action and alert limits for monitoring, and of control charts which show trends. It is possible that in certain situations the full range of testing done in the PQ runs would be repeated. However, the value of validation is that consistency has been demonstrated, and the emphasis in monitoring should be tests that might indicate a process change.

Change Control

Validated cleaning processes should be subject to change control. Changes include unplanned and planned changes. Examples of unplanned changes include the failure of a process pump, the clogging of a spray device, and the discontinuance of a cleaning agent by a supplier. The keys to change control are to evaluate the effects of any change, correct the changed item (if possible), implement any increased monitoring as needed, and document the procedure. For example, failure of a pump in a CIP skid may just require a switch of like for like, IQ on the new pump, optionally OQ on the new pump, and proper documentation. Clogging of a spray device may require cleaning of the device and an investigation of the cause of clogging. This should be followed by preventive measures, such as installation of a filter screen to remove material with the potential to clog and some kind of preventive maintenance to regularly clean the screen and inspect the spray device. In both these cases, it may not be necessary to repeat a PQ run. On the other hand, a slight compositional change of the cleaning agent may require laboratory studies to suggest equivalence, followed by one PQ run to confirm equivalence. A change in the manufacturing process itself, and the possible effect of such a change on the cleanability of the equipment, should not be neglected when considering change control for a cleaning process. A change such as increased processing temperature may modify the condition of the soil and, therefore, make it more difficult to clean. In all cases documentation of changes according to a change control SOP is mandatory.

Training

Training operators in the cleaning SOP is an important part of validation maintenance, particularly for manual cleaning methods. Training in a manual method should include a classroom discussion of the method, observation of the SOP being performed by a trained operator, and then demonstration of proficiency by performance of the SOP by the trainee. Training should always follow revision of the SOP, and retraining should follow any deviations that were attributable to operator error.

Revalidation

There are two aspects to revalidation of a previously validated cleaning process. First is revalidation upon any significant change. What is "significant" is a matter of professional judgment. However, a change in cleaning method, such as from manual cleaning to automated cleaning will generally require revalidation even though the cleaning agent and process parameters are the same. In essence this is not really revalidation but rather validation of a new cleaning process. The other aspect of revalidation is based on the evaluation of the consistency and control of a cleaning process on a regular basis to confirm that the process is still under control. The time of this periodic revalidation should be specified in a cleaning validation policy (such as in the cleaning validation master plan), and typically is every one or two years. Such a periodic revalidation involves an evaluation of the monitoring data, change control, cleaning process deviations, and quality records of products manufactured after the cleaning process. If the monitoring data is adequate, the change control is minor, any deviations have had attributable to corrected causes, and there have been no product quality problems possibly related to cleaning, then all this information is suggestive of a cleaning process that is still under control. In such a case it is possible to document such findings in a revalidation report with a conclusion that the cleaning process is still under control and that the original validation work is sill applicable. On the other hand, if the monitoring data show continual trends which require corrections, if numerous individual changes have been made (each of which was acceptable) but the overall cleaning process is now seen as significantly different, if deviations in the cleaning process have either not been attributable to a cause or the cause has not been corrected, and/or if there have been product quality issues related to the cleaning process, then such an investigation may result in a repeat of one or more PQ runs. In such a case, usually there will be some laboratory or pilot scale evaluations before PQ runs are performed.

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